Meisenheimer Complexes: Reaction of Methoxide Ions with 2-Chloro-4,6-Dinitroanisole in Methanol and in Methanol–Dimethyl Sulphoxide

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The reaction of methoxide ions with 2-chloro-4,6-dinitroanisole (VI) has been studied kinetically in methanol and in various MeOH–dimethyl sulphoxide (DMSO) mixtures by the stopped-flow method. When the DMSO concentration reaches 70% (w/w), the appearance of the classical Meisenheimer 1,1-complex (VII) is preceded by the fast formation of the thermodynamically less stable 1,3-complex (VIII) which is produced by the attack of MeO^- on the unsubstituted C-3 of (VI), and undergoes a rapid conversion into (VII). The interaction becomes still more complicated in the mixtures whose DMSO concentration is greater than 85%, where the initial formation of the 1,5-complex (IX) can be observed. The rate and equilibrium constants for the formation of the three sorts of complexes (VII) (k_3, K_3), (VIII) (k_2, K_2), and (IX) (k_1, K_1), and those for their decomposition (k_{-3}, k_{-2}, and k_{-1}) have been determined. These data shed some light on the mechanism of the interaction and the factors affecting the stabilities of the complexes. Thus, it can be seen that the greater thermodynamic stability of the 1,3-complex (VIII) with respect to that of the 1,5-complex (IX) is essentially because it benefits from the strong delocalizing effect of a *para*-nitro-group.

Servis [1] and Gold *et al.*[2] have shown by n.m.r. spectroscopy that the reaction of methoxide ions with 2,4,6-trinitroanisole in dimethyl sulphoxide (DMSO) results in the initial formation of the 1,3-complex (I) followed by the slow appearance of the more stable 1,1-complex (II). Analogous findings have been reported later with many other substituted 4-X-2,6-dinitroanisoles.[3,4] The rate and equilibrium constants have been determined in MeOH–DMSO mixtures for the two sorts of complexes.[5,6] In agreement with the qualitative n.m.r. observations, one can see that 1,3-complexes are formed and decompose rapidly whereas the more stable 1,1-complexes are formed slowly. The DMSO concentration in the solvent mixture and the nature of the substituent X appear to be of major importance in the interaction.

In the case of substituted 2-X-4,6-dinitroanisoles, the formation of 1,3-complexes (III) has also been observed [3] but, since the non-substituted 3- and 5-positions are not equivalent, it could be expected that the methoxide ion attack would also occur on the 5-carbon leading to 1,5-complexes (IV). Indeed, we have recently confirmed this fact by n.m.r.[7,8] but no kinetic measurements were

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[1] (*a*) K. L. Servis, *J. Amer. Chem. Soc.*, 1965, **87**, 5495; *b*) 1967, **89**, 1508.

[2] M. R. Crampton and V. Gold, *J. Chem. Soc.* (*B*), 1966, 893.

[3] J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, 1969, **34**, 689.

[4] F. Millot and F. Terrier, *Bull. Soc. chim. France*, 1969, 2694.

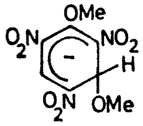
[5] F. Terrier and F. Millot, *Bull. Soc. chim. France*, 1970, 1743.

[6] F. Terrier, C. Dearing, and R. Schaal, ' Reaction Transition States,' Gordon and Breach, London, in the press.

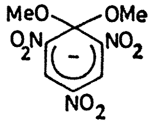
[7] F. Terrier and M. P. Simonnin, *Bull. Soc. chim. France*, 1971, 677.

[8] F. Terrier, J. C. Halle, and M. P. Simonnin, *Org. Magnetic Resonance*, 1971, **3**, 361.

performed on such compounds. We now report a kinetic study, by the stopped-flow method, of the interaction of methoxide ions with 2-chloro-4,6-dinitroanisole (VI) in MeOH–DMSO mixtures.



(I)



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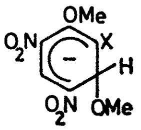

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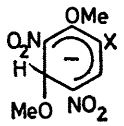

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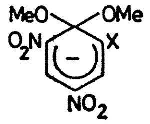


(V)

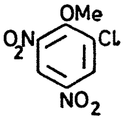
EXPERIMENTAL

Materials.—2-Chloro-4,6-dinitroanisole, m.p. 36° (lit.,[9] 36—37°), was prepared from 2-chloro-4-nitroanisole by the method of Philipp and Reverdin.[9a] The structure of the pure product was confirmed by elemental analysis and n.m.r. spectroscopy.[8,9c] Solutions of potassium methoxide in methanolic DMSO were freshly prepared from the purified solvents by appropriate dilutions.

Rate and Equilibrium Measurements.—Stopped-flow determinations were performed at 20 °C on a Durrum stopped-flow spectrophotometer the cell compartment of which was thermostatted within ±1 °C. The kinetic measurements were made between 500 and 580 nm, depending on the MeOH–DMSO mixture used and the equilibrium under consideration.

RESULTS

Mixtures Rich in Methanol.—In methanol and in MeOH–DMSO mixtures, the DMSO content of which is less than about 70% (w/w), the reaction of methoxide ions with 2-chloro-4,6-dinitroanisole (VI) gives directly [process (1)] the stable 1,1-complex (VII) whose structure has been confirmed by n.m.r. spectroscopy.[8] The appearance of this complex has been followed spectrophotometrically at 500 nm, most often by the stopped-flow method, though sometimes the usual kinetic methods were convenient.



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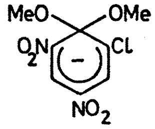
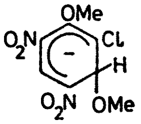
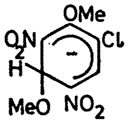


(VII)



(VIII)



(IX)

$$\text{(VI)} + \text{MeO}^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \text{(VII)} \qquad (1)$$

Since the concentration of (VI) was always very small (*ca.* 2×10^{-5}M) with respect to the methoxide ion concentrations of 5×10^{-4}—10^{-1}M used, the amount of base consumed in establishing the equilibrium could be neglected and pseudo first-order relationships were obtained in all cases. The variations of the apparent rate constant λ_3 as a function of the base concentration b obey equation (2) as

$$\lambda_3 = k_{-3} + k_3 b \qquad (2)$$

shown in Figure 1. From the slopes and intercepts of the observed straight lines in the mixtures whose DMSO content is equal to or less than 57·5% (w/w), the rate constants k_3 and k_{-3} were obtained for the formation and the decomposition of (VII), and consequently the equilibrium constant K_3. Above 57·5% DMSO, k_{-3} becomes too small for an accurate determination from the intercepts and the graphs give only k_3.

The values of k_{-3} thus obtained in the mixtures with lower DMSO content agree very well with those determined by following directly the decomposition of the solid complex which is easily isolable.[8]

Mixtures with 70—85% *DMSO.*—In the two mixtures containing 76 and 84·8% DMSO which we have studied, the kinetic curves obtained by the stopped-flow method show clearly that the appearance of the 1,1-complex (VII) is preceded by the fast formation of a thermodynamically less stable species which undergoes a complete and rapid conversion into (VII). By use of n.m.r. we were able [8] to identify this species as the 1,3-complex (VIII) due to the initial attack by MeO^- on C-3 of 2-chloro-4,6-dinitroanisole.

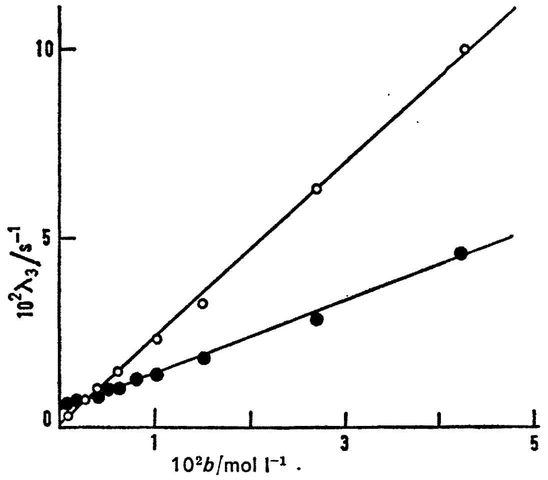
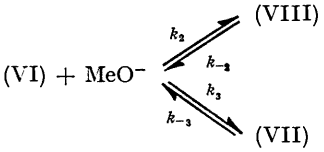


FIGURE 1 Plot of λ_3 against b for the appearance of the 1,1-complex in, ●, 37, and ○, 47·5% DMSO (by weight)

The kinetic process (3) of two competitive reactions which corresponds to this interaction involves in fact two separate steps, whatever the base concentration of the solution may be. The first step is the attainment of



$$\text{(VI)} + \text{MeO}^- \begin{array}{l} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{(VIII)} \\ \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \text{(VII)} \end{array} \qquad (3)$$

equilibrium for complex (VIII) with an apparent rate constant λ_2 given by equation (4). The rate constants k_2 and k_{-2}, and thus the equilibrium constant K_2, were determined, as k_3 and k_{-3} from equation (2), from the rate measurements performed at 540 nm.

$$\lambda_2 = k_{-2} + k_2 b \qquad (4)$$

[9] (*a*) K. Philipp and F. Reverdin, *Ber.*, 1905, **38**, 3774; (*b*) A. F. Holleman, W. J. de Mooy, and J. Terweel, *Rec. Trav. chim.*, 1916, **35**, 1; (*c*) F. Terrier, *Ann. Chim.* (*France*), 1969, 153.

The second step is the slower equilibrium formation of (VII) from the molecule which is considered as being in instantaneous equilibrium with (VIII). As previously shown,[5,6,10b,11] the rate equation again gives pseudo first-order relationships with an apparent rate constant λ_3' expressed by equation (5), which reduces to equation (6)

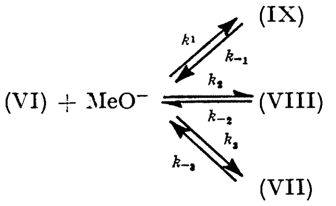
$$\lambda_3' = k_{-3}\left(\frac{1 + K_2b + K_3b}{1 + K_2b}\right) \qquad (5)$$

$$\lambda_3' = k_{-3}\left(\frac{1 + K_3b}{1 + K_2b}\right) = \frac{\lambda_3}{1 + K_2b}\ (K_2 \ll K_3) \qquad (6)$$

because the equilibrium constant K_3 is much greater than K_2. Thus, from the measured values of λ_3', the values of the apparent rate constant λ_3 could be calculated which would be observed in the same experimental conditions if the stable 1,1-complex (VII) were always formed directly by reaction of MeO$^-$ with (VI). Unfortunately, only the rate constant k_3 could be determined by plotting the values of λ_3 against the base concentration.

Mixtures very rich in DMSO.—As soon as the DMSO content reaches *ca.* 85% by weight, the appearance of the 1,3-complex is itself preceded by the formation of another complex whose lifetime is too short for n.m.r. detection.[8] However, this new complex can be reasonably considered to be the 1,5-complex (IX) formed by the attack of MeO$^-$ on the unsubstituted C-5 of (VI). Indeed, we have recently succeeded in identifying by n.m.r. such 1,5-complexes with 2-cyano- and 2-trifluoromethyl-4,6-dinitroanisoles.[8]

When the base concentration is kept below 2×10^{-3}M in the mixture containing 92·6% DMSO, three sufficiently separated steps are observed for this interaction which involves theoretically three competitive reactions according to process (7). Above 2×10^{-3}M, the formation of the 1,5-complex interferes rather strongly with that of the 1,3-complex. Consequently, the attainment of the equilibrium for the formation of (IX) has been followed in a rather limited range of base concentrations (5×10^{-4}—2×10^{-3}M). In spite of these difficulties, a graph of the apparent rate constant λ_1 [equation (8)] with respect to the base concentration gives a fairly good straight line (Figure 2) from which we were able to obtain the rate constants k_1 and k_{-1} and thus the equilibrium constant K_1. Using this value, the spectrum of pure 1,5-complex (IX) was calculated from the absorbance measured at 2×10^{-3}M (Figure 3).



(7)

Under the same experimental conditions, the formation of the 1,3-complex (VIII) occurs from the molecule which is in rapid equilibrium with (IX). The expression of the apparent rate constant λ_2' for this step [equation (9)] is

$$\lambda_1 = k_{-1} + k_1b \qquad (8)$$

$$\lambda_2' = k_{-2}\left(\frac{1 + K_1b + K_2b}{1 + K_1b}\right) \qquad (9)$$

similar to that of λ_3' [equation (5)] but cannot be simplified because the equilibrium constant K_2 is only *ca.* 13-fold greater than K_1. By combining the experimental values obtained for λ_2' at different base concentrations, it was possible to calculate a mean value for the rate constants k_2 and k_{-2} and thus for K_2. Since the conversion of (IX) into (VIII) is not complete, we had to evaluate the spectrum of this latter complex which is shown on Figure 3.

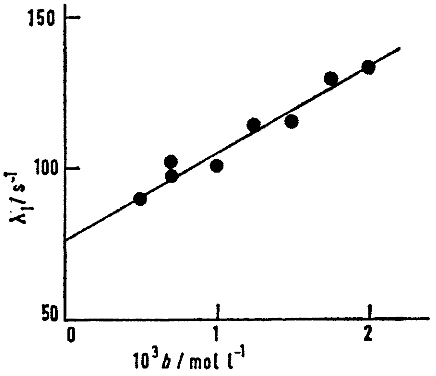


FIGURE 2 Plot of λ_1 against b for the appearance of the 1,5-complex in 92·6% DMSO (by weight)

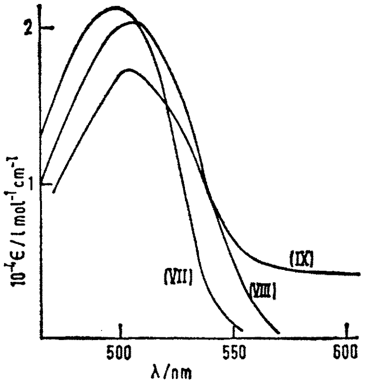


FIGURE 3 Absorption spectra of 1,1- (VII), 1,3- (VIII), and 1,5-complexes (IX) in 92·6% DMSO (by weight)

The last step is the slow equilibrium formation of the 1,1-complex (VII) from the molecule which is assumed to be in fast equilibrium with the 1,5- and 1,3-complexes (IX) and (VIII). The apparent rate constant λ_3'' is given by equation (10) but taking into consideration that the equilibrium constant K_3 is much greater than K_1 and K_2, the simplified equation (11) could be used. Since a plot of

$$\lambda_3'' = k_{-3}\left(\frac{1 + K_1b + K_2b + K_3b}{1 + K_1b + K_2b}\right) \qquad (10)$$

$$\lambda_3'' = k_{-3}\left(\frac{1 + K_3b}{1 + K_1b + K_2b}\right) \qquad (11)$$

λ_3'' against the base concentration exhibits only the straight line of slope 0, consistent with the maximum value for λ_3'' [equation (12)], we were only able, knowing K_1 and K_2, to estimate the rate constant k_3 for the formation of (VII).

$$\lambda_3''(\text{max.}) = k_3/(K_1 + K_2) \qquad (12)$$

[10] (*a*) C. F. Bernasconi, *J. Amer. Chem. Soc.*, 1970, **92**, 4682; (*b*) 1971, **93**, 6975.

[11] F. Terrier and F. Millot, *Bull. Soc. chim. France*, 1971, 3897.

Table 1 summarizes the various rate coefficients and equilibrium constants which were determined at 20 °C in different MeOH–DMSO mixtures. The results are averages of at least two independent determinations and the error in the reported rate constants is estimated to be *ca.* ±5% except in the mixture containing 92·6% DMSO. In this case, the error can reach ±20% because of the experimental difficulties just discussed; however in spite of their uncertainty, the rate coefficients are good enough for a quantitative treatment of the interaction in this mixture.

TABLE 1

Rate and equilibrium constants for the reaction of 2-chloro-4,6-dinitroanisole with methoxide ion in various MeOH–DMSO mixtures at 20 °C

	1,1-Complex (VII)			1,3-Complex (VIII)			1,5-Complex (IX)		
Solvent composition % DMSO by weight	k_3/ l mol⁻¹ s⁻¹	10^4k_{-3}/ s⁻¹	K_3/ l mol⁻¹	k_2/ l mol⁻¹ s⁻¹	k_{-2}/ s⁻¹	K_2/ l mol⁻¹	k_1/ l mol⁻¹ s⁻¹	k_{-1}/ s⁻¹	K_1/ l mol⁻¹
0	0·28	360	7·8						
13·35	0·39	191	20·4						
25·3	0·605	112	54						
37	1·1	60	183						
47·5	2·24	26·4	850						
57·5	5·5	10·7	5150						
67	13·8								
76	37			795	21	38			
84·8	105			2900	8·1	358			
92·6	410	≃0·1 [a]	$4·1 \times 10^7$ [b]	10,000	2	5000	29,000	76	382

[a] Data estimated by taking into account that the DMSO content affects similarly the rate constant for the decomposition of Meisenheimer complexes (see Figure 4 and Discussion). [b] Calculated by using the estimated value for k_{-3}.

DISCUSSION

With addition of DMSO to the methanolic solutions there is a strong increase in the thermodynamic stability of complexes (VII) and (VIII), associated with an increase in the rate constants for their formation and a decrease in the rate constants for their decomposition. These findings are similar to those observed for the formation of various Meisenheimer complexes and have already been discussed.[5,6,12,13] However, it is noteworthy that DMSO appears to influence similarly the rate constants for the formation and the decomposition of a number of Meisenheimer complexes formed from molecules, such as 4-X-2,6-dinitro- or 2-X-4,6-dinitroanisole whose structures are similar; as shown in Figure 4, similar curves are observed by plotting the variations of rate coefficients *versus* the DMSO content for these compounds. This similarity is very useful because it allows the value for the rate constant k_{-3} for the decomposition of the 1,1-complex (VII) to be estimated by extrapolation in the mixture containing 92·6% DMSO where only the rate constant k_3 for its formation can be obtained from kinetic data. By using this estimated value (Table 1) we are able to analyse quantitatively the formation of the three sorts of complexes in this mixture.

From the comparison of the rate constants for the formation and the decomposition of complexes (VII)—(IX), it is clear that the reactions of 2-chloro-4,6-dinitroanisole to give the 1,5- and 1,3-complexes which both involve a nucleophilic attack on a non-substituted carbon atom, are very different from the reaction to give the 1,1-complex which involves addition of base at a carbon atom bearing a methoxy-group. On the one hand, (VIII) and (IX) form and decompose rapidly, so that their thermodynamic stability is relatively low; these two complexes can be observed only in the mixtures rich in DMSO where the equilibrium constants K_1 and K_2 for their formation are sufficiently large. On the other hand, the 1,1-complex formation is slow but has a very high equilibrium constant and it can be studied in the absence of DMSO cosolvent.

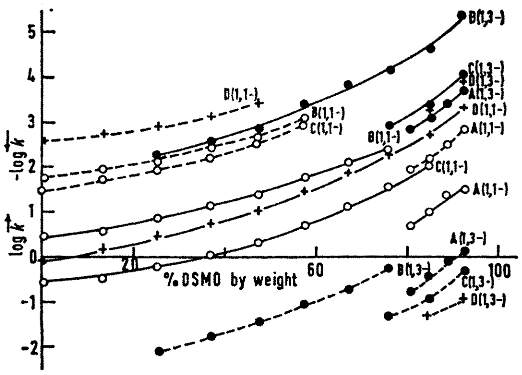


FIGURE 4 Effect of DMSO content on rate constants for the formation $\overrightarrow{k}$ (continuous lines) and for the decomposition $\overleftarrow{k}$ (broken lines) of various Meisenheimer 1,1- and 1,3-complexes; A, 4-chloro-2,6-dinitroanisole; B, 4-cyano-2,6-dinitroanisole; C, 2-chloro-4,6-dinitroanisole; and D, 2,4-dinitro-1-methoxynaphthalene

These results agree very well with the general features observed for such nucleophilic attacks at a substituted or unsubstituted ring carbon atom of 2,4,6-trinitro-[1,2,14] and 4-X-2,6-dinitro-anisole[5,6] and previously interpreted by Gold and Crampton[2,14c] by assuming that the main factor would be the steric strain in the transition state leading to the 1,1-complex. Steric effects should be comparatively unimportant for addition of base to a

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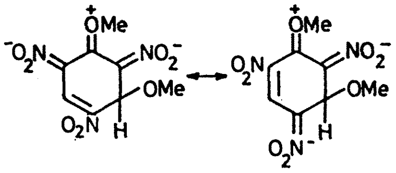
[12] (*a*) E. J. Fendler, J. H. Fendler, C. E. Griffin, and J. W. Larsen, *J. Org. Chem.*, 1970, **35**, 287; (*b*) J. W. Larsen, K. Amin, and J. H. Fendler, *J. Amer. Chem. Soc.*, 1971, **93**, 2910.

[13] M. R. Crampton, *J. Chem. Soc.* (*B*), 1968, 1208.

[14] (*a*) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, 1966, **16**, 61; (*b*) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev.*, 1968, **22**, 123; (*c*) M. R. Crampton, *Adv. Phys. Org. Chem.*, 1969, **7**, 211; (*d*) M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667.

ring carbon atom carrying hydrogen. Thus, the formation of the 1,3-complex, and consequently for the same reason, of the 1,5-complex, will be faster than the formation of the 1,1-complex whose greater thermodynamic stability is attributed to the release of steric strain from the molecule and to the fact that the two methoxy-groups have a large stabilizing effect on the tetrahedral C-1. According to a recent suggestion by Bernasconi [10] for 2,4,6-trinitroanisole, the principal factor for this behaviour might however be resonance stabilization involving the methoxy-group which, in contrast with the 1,1-complex, can benefit not only the molecule but also the 1,3-complex [(Xa) ⟷ (Xb)], and obviously the 1,5-complex in the case of 2-X-4,6-dinitroanisole as well as the transition states leading to the formation of these two complexes. Indeed, as it has been noted,[6,11] these two factors are dependent on the position and the nature of the X-substituent and it seems likely to us that they may interact in the general case of 4-X-2,6-dinitro- and 2-X-4,6-dinitro-anisole.



(Xa) (Xb)

In a comparison of the formation of the 1,5- (IX) with that of the 1,3-complex (VIII), the situation is different in that both reactions involve addition of base at a ring carbon atom carrying hydrogen. Whereas the rate constants for the formation of these two complexes are somewhat similar ($k_1/k_2 = 2{\cdot}9$), the rate constant for the decomposition of (IX) is about 40-fold greater than that for the decomposition of (VIII).* Consequently, (IX) appears to be thermodynamically less stable than (VIII) ($K_1/K_2 = 0{\cdot}076$).

This result which agrees very well with the previous qualitative observations we have made by n.m.r. spectroscopy for 2-cyano- and 2-trifluoromethyl-4,6-dinitroanisole,[7,8] ought probably to be attributed to the fact that the 1,5-complex does not benefit from the strong delocalizing effect of a *para*-nitro-group as opposed to the 1,3-complex. This view is supported by the behaviour of 3,5-dinitrobenzonitrile (XI) and 3,5-dinitropyridine (XIV) the two sorts of unsubstituted positions in which exhibit, to a first approximation, the same structural features as the 3- and 5-positions of 2-X-4,6-dinitroanisoles such as 2-chloro-4,6-dinitroanisole. Indeed, the reaction of these substrates with methoxide [15,16a] or hydroxide ions [15,16b] in MeOH- or H_2O–DMSO mixtures results in the faster initial formation of complexes (XII) and (XV) whose structure is similar to that of the 1,5-complexes (IV) followed by the slower appearance of the more stable complexes (XIII) and (XVI) whose sp^3-carbon atom is *para* to a nitro-group as in the 1,3-complexes (III). As can be seen from Tables 2 and 3 which give a few results concerning these interactions in the H_2O–DMSO mixtures, the rate constants for the formation of the two sorts of complexes (XII) and (XIII) [or (XV) and (XVI)] are somewhat similar, so that the lower thermodynamic stability of (XII) and (XV) with respect to that of (XIII) and (XVI) is largely due to their greater rate of decomposition. It is thus apparent that the greater stabilizing effect of nitro-groups in the *para* than in the *ortho* position is the principal factor governing the relative stabilities of 1,5- and 1,3-complexes formed from 2-chloro-4,6-dinitroanisole and more generally from 2-X-4,6-dinitroanisoles.

TABLE 2

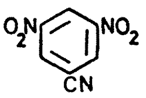
Reaction of hydroxide ion with 3,5-dinitrobenzonitrile in 46·4% H_2O–53·6% DMSO (by weight) at 20 °C. Values of k_1, k_{-1}, and K_1 for complex (XII) and k_2, k_{-2}, and K_2 for complex (XIII)

k_1/ l mol^{-1} s^{-1}	k_{-1}/ s^{-1}	K_1/ l mol^{-1}	k_2/ l mol^{-1} s^{-1}	k_{-2}/ s^{-1}	K_2/ l mol^{-1}
272	7·7	35·3	112	0·3	373

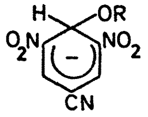
TABLE 3

Reaction of hydroxide ion with 3,5-dinitropyridine in 58·6% H_2O–41·4% DMSO (by weight) at 20 °C. Values of k_1, k_{-1}, and K_1 for complex (XV) and k_2, k_{-2}, and K_2 for complex (XVI)

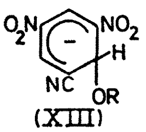
k_1/ l mol^{-1} s^{-1}	k_{-1}/ s^{-1}	K_1/ l mol^{-1}	k_2/ l mol^{-1} s^{-1}	k_{-2}/ s^{-1}	K_2/ l mol^{-1}
345	9	38·4	138	0·12	1150



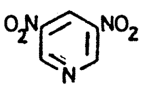
(XI)



(XII)



(XIII)



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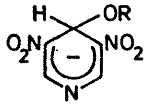
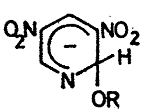


(XV)



(XVI)

R = H,Me

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* At the lowest base concentrations used in the mixture containing 92·6% DMSO, the difference in the rates of decomposition of (VIII) and (IX) causes the observed rate of formation of (IX) to be significantly greater than that of (VIII), thus allowing the determination of the rate and equilibrium parameters for the two reactions (see Results section).

[15] F. Terrier, F. Millot, and M. P. Simonnin, *Tetrahedron Letters*, 1971, 2933.

[16] (*a*) R. Schaal, F. Terrier, J. C. Halle, and A. P. Chatrousse, *Tetrahedron Letters*, 1970, 1393; (*b*) F. Terrier and A. P. Chatrousse, unpublished results.